Remarks/Arguments

The specification has been amended to add appropriate sequence identifiers pursuant to 37 C.F.R. § 1.821 (a)(1) and (a)(2).

Prior to the present amendments, claims 1-41 were pending in this application. Claims 17 and 20-41 were withdrawn from consideration, claims 1-3 were rejected, and claims 4-16, 18 and 19 were objected to. Claims 7-12, 14, and 16-17 have been canceled, and claims 1, 3, 4, 13, and 15 have been amended. Support for the amendment of claim 1 is at least at page 20, line 20, original claim 15 and original claim 14. Claims 3, 4 and 13 have been made dependent from claim 1 alone. Claim 15 has been amended for consistency with claim 1 and made dependent from it.

All amendments and cancellations were made without prejudice or disclaimer, and without acquiescence to any of the rejections or the Examiner's reasoning advanced in support of the rejections. Applicants explicitly reserve the right to pursue any deleted subject matter in one or more continuing applications.

Election/Restriction

Applicants note the finality of the restriction requirement with regard to the inventions of Groups I-III.

Applicants also note the maintenance of the restriction requirement with respect to the various types of antagonists.

Applicants continue to disagree with the finding that a unity of invention does not exist for the various types of nucleotide antagonists, and respectfully request that the Examiner reconsider his position in that regard.

The Examiner justifies the restriction between the three different classes of "nucleotide agents" by pointing out structural and functional differences between them.

However, solely the fact that differences can be observed between different species should not necessarily prevent them from being regarded as unified. Otherwise no species with any structural or functional distinctions could ever be unified, and so no generic claim could every be allowed.

As the Examiner correctly notes, MPEP 803.02 cites:

> *"Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility."*

This establishes that unity should be acknowledged if a common utility and a substantial structural feature are shared by the various species. This is rather different from the Examiner's apparent position, which seems to be that unity cannot be acknowledged if there is any identifiable difference between the various species. The nucleotide antagonists meet the proper unity standard, as expressed in MPEP 803.02, because they share the utility of antagonizing GPC5, and comprise a nucleic acid sequence complementary to the sequence of GPC5 mRNA or pre-mRNA.

The Examiner distinguishes antisense and dsRNA methods as follows:

> *"With respect to the nucleotide agents (i.e., antisense RNA, double stranded RNAi/siRNA, ribozyme), its is noted that antisense RNAs, double stranded RNAs and ribozymes do not share a substantial structural feature essential to their utility because . . . they are structurally distinct molecules as antisense RNAs are single stranded while double stranded RNAs are double stranded . . . Furthermore, each of the nucleotide antagonists utilize different biological pathways. . . . Double stranded RNAs utilize the enzyme RISC while . . . antisense RNAs do not. Antisense RNAs bind with complementary mRNAs and physically obstructing translation."*

Ribozymes have been deleted from the claims, so those distinctions are moot.

From a structural perspective, antisense and dsRNA are both nucleic acids which consist of or comprise a strand having a sequence complementary to the mRNA whose expression is to be inhibited. This represents a substantial structural similarity as required by the passage of the

MPEP cited above. The fact that dsRNA also comprises a second strand does not detract from this structural similarity.

From a functional perspective, both types of agent act to reduce expression of GPC5, which has utility in inhibiting target cell proliferation. The ultimate utility is therefore the same, as required by the MPEP, regardless of whether the two agents share the same mechanism of action. Indeed, the mechanism of action is irrelevant for unity considerations.

In any event, the mechanisms of action of the antisense and dsRNA are indeed much more similar than the Examiner believes, as explained in more detail below.

It is true that some antisense molecules bind to complementary mRNAs and physically obstruct their translation by the ribosome. However, this is not the only mechanism by which they work, and probably not even the predominant mechanism.

The enclosed review (Dean and Bennett, Oncogene (2003) 22, 9087-9096) explains that:

> *"The best-characterized antisense mechanism results in cleavage of the targeted RNA by endogenous cellular nucleases, such as Rnase H or the nuclease associated with the RNA interference mechanism . . .*
>
> *Rnase H is a family of ubiquitously expressed enzymes that cleave the RNA strand of an RNA-DNA heteroduplex, with at least two forms found in mammalian cells . . . Antisense oligonucleotides that inhibit gene expression by an Rnase H-dependent mechanism of action (Figure 1) contain a continuous segment of at least five to seven DNAlike nucleotides to support Rnase H activity . . . Most of the antisense drugs currently in clinical trials utilize the Rnase H mechanism (Table 1). As such, oligonucleotides that work through an Rnase H mechanism of action are well characterized in terms of their pharmacology, pharmacokinetis and toxicity."* (Page 9087, col. 2 - page 9088, col. 1)

This is also described in the legend to Figure 1.

The review goes on to describe the mechanism by which RNAi inhibits expression. As the Examiner points out, this involves the so-called RISC complex, rather than Rnase H. However, the authors conclude that:

"RNA interference is an antisense mechanism of action, as ultimately a single-strand RNA molecule binds to the target RNA molecule by Watson-Crick base pairing rules and recruits a ribonuclease that degrades the target RNA." (Page 9088, col. 1)

Thus, the mechanisms by which antisense and dsRNAs actually work are essentially similar. They both involve hybridization of a single-stranded nucleic acid to a complementary mRNA sequence which results in the degradation of the mRNA by Rnase activity.

For these reasons and because claim 1, and all claims dependent thereon, now recite that the antisense RNA, antisense DNA and dsDNA comprise a nucleic acid sequence complementary to the sequence of GPC5 mRNA or pre-mRNA, the Examiner is respectfully requested to withdraw the restriction requirement for these species of nucleotide antagonists, and examine antisense RNA, antisense DNA and dsRNA in the present application.

Specification - Sequence Compliance

The disclosure was objected to since pages 39-40 of the specification contain sequences that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. 1.821(a)(a) and (a)(2) without sequence identifiers. According to the Office Action, "[i]t is assumed that the indicated sequence also do not appear in the Paper Sequence and CRF, as required."

The latter assumption is incorrect. The sequences listed on pages 39-40 of the specification (as well as the sequence listed on page 25, not mentioned in the Office Action) are included in the Sequence Listing submitted on October 19, 2007, both in paper and in a computer readable form. In the foregoing amendments, the specification has been amended to include the appropriate SEQ ID Nos. Accordingly, this application is full compliance with the sequence rules, and the submission of a new Paper Sequence and CRF is not necessary. Nonetheless, a copy of the Notice to Comply attached to the Office Action is returned with the present submission, noting that the Notice issued in error.

Claim Objections

Claims 4-16, 18 and 19 are objected to under 37 CFR 1.75(c) as allegedly being in improper form because of multiple dependent claim cannot depend from any other multiple dependent claim. This objection is moot in view of the amendments to the claims.

Claim Rejections - 35 USC § 112

Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner notes that "to provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus," and asserts that there is "no requirement that the molecules have any structural relationship." The Examiner further notes that "*the specification has only provided an adequate description of the nucleotide sequence that is complementary to the sequence of the GPC5 mRNA or pre-mRNA and that inhibit the expression of GPC5.*"

Without acquiescence to the Examiner's position and solely to expedite prosecution, the claims have been amended to recite the common structural and functional features for which adequate written description has been acknowledged. Accordingly, the Examiner is respectfully requested to withdraw the present rejection.

Conclusion

All claims pending in this application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to **Deposit Account No. 50-2387**, referencing Attorney Docket No. **MWB-0004 (24117.005)**.

Respectfully submitted.

January 5, 2010

By: Electronic Signature: /GINGER R. DREGER/
Registration No. 33,055

ARNOLD & PORTER LLP
555 Twelfth Street, NW
Washington, D.C. 20004-1206
Telephone: +1 202.942.5000
Facsimile: +1 202.942.5999

Notice to Comply	Application No.	Applicant(s)	
	Examiner J. Eric Angell	Art Unit 1635	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other: _

Applicant Must Provide:

☒ An initial or **substitute** computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or **substitute** paper copy of the "Sequence Listing", as well as an amendment directing its entry into the **specification**.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216 or (703) 308-2923
For CRF Submission Help, call (703) 308-4212
PatentIn Software Program Support
Technical Assistance.....703-287-0200
To Purchase PatentIn Software.....703-306-2600

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR REPLY